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CLINICAL TRIAL

Ultrasound-guided breast-conserving surgery for early-stage palpable and nonpalpable invasive breast cancer: decreased excision volume at unchanged tumor-free resection margin

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Abstract Ultrasound guidance (USG) during breast-conserving surgery improves tumor-free surgical resection margins. The objective of this study was to evaluate whether USG reduces resection volumes without compromising margin status. 134 patients with palpable or nonpalpable $T_{1–2}N_{0–1}$ invasive breast cancer were treated with USG and compared with a historical reference control group (CON) consisting of palpation-guided (PAG) or wire-guided localization (WIG) breast-conserving surgery. Primary outcomes were excess resection volume and clear margin status, and secondary outcome was re-excision rate. 66 patients underwent USG. In the CON group ($n = 68$), PAG was performed in 24 (35 %) and WIG in 44 (64 %) patients. Median excision volume [39 (IQR 20–66) vs 56 (38–94) cm^3; $p = 0.001$] and median calculated resection ratio [1.7 (1.0–2.9) vs 2.8 (1.4–4.6) ($p = 0.005$)] were significantly smaller in the USG than in the CON group. Median minimal distance to the resection margin [4 mm (IQR 2–5 mm) vs 2 mm (1–4 mm), $p = 0.004$] was significantly larger. Clear resection margins were achieved in 58 of the USG patients (88 %) and in 58 of the CON patients (86 %) ($p = 0.91$); this was true in patients with palpable as well as nonpalpable lesions. Reexcision was needed in 6.1 and 7.2 % respectively. Relative risk for re-excision in the USG group was 0.82 (95 % CI 0.23–2.93). In patients with palpable and nonpalpable breast cancers, USG allows for lower excision volume and reduced resection of healthy breast tissue, without increased re-excision rate.

Keywords Breast cancer · Breast-conserving surgery · Ultrasound

Introduction

One of the primary goals of breast-conserving surgery (BCS) in patients with early-stage breast cancer is to completely remove the tumor while preserving as much healthy tissue as possible to achieve a satisfactory cosmetic outcome [1–7]. Clear resection margins are of the utmost importance because positive margins lead to higher recurrence rates in patients with invasive carcinoma and therefore require re-excision or mastectomy [6, 7]. This in turn may lead to increased wound infection rates and patient stress [1, 8, 9].

Accurate intraoperative guidance is essential to achieving complete tumor excision and optimal resection volume in BCS. In case of palpable breast carcinomas, the surgeon uses preoperative diagnostic imaging and intraoperative palpation to guide the operation. However, palpation alone is insufficient to differentiate malignant tissue from fibrosis or dense breast parenchyma [4, 10]. In case of nonpalpable tumors, wire-guided localization is the standard technique to guide the operation. This technique, however, carries several disadvantages, including discomfort on insertion, the possibility of wire dislocation and migration, and the need for a postexcision specimen mammography [11, 12].

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Ultrasound-guided BCS, during which the ultrasound is used to intraoperatively visualize the tumor, does not carry these disadvantages; moreover, it allows surgery to be performed with greater precision [13–18].

Several studies have been published on ultrasound-guided BCS, focusing on margin status as the outcome of breast-conserving surgery for both palpable and nonpalpable breast cancers [13–16]. Recent meta-analyses published by Pan et al. and by Ahmed et al. demonstrated the benefits of ultrasound guidance over palpation-guided BCS or wire-guided localization with respect to tumor-free resection margins [17, 19]. However, few studies have focused on the optimal tissue resection volume without sacrificing healthy breast tissue as an outcome of the different surgical techniques. It is reasonable to assume that more precise intraoperative guidance leads to a reduction in excision volume and thereby to an improved cosmetic outcome and accompanying patient satisfaction [20]. Therefore, the objective of this study was to evaluate whether ultrasound-guided BCS results in smaller resection volumes and a reduction of healthy breast tissue resection compared with palpation-guided BCS or wire-guided localization, without compromising margin status in patients with early-stage breast cancer. Since many studies have been performed on patients with either palpable or nonpalpable lesions, a second objective was to assess whether there was a difference in the hypothesized reduction in resection volume between patients with palpable and nonpalpable lesions.

Methods

For this study, a prospective cohort of patients with histologically proven early-stage $T_{1–2}N_{0–1}$ invasive palpable and nonpalpable breast cancer scheduled to undergo ultrasound-guided BCS was enrolled between July, 2013 and July, 2014. We compared them with a historical cohort of patients treated with conventional surgery (palpation-guided BCS or wire-guided localization) between February 2012 and April 2013. Patients with preoperatively diagnosed ductal carcinoma in situ (DCIS) were excluded. The institutional review board of Gelre Hospital Apeldoorn, the Netherlands, approved the study. The requirement to obtain informed consent was waived.

Breast cancer was diagnosed by physical examination, mammography, and ultrasonography of the breast and axilla, followed by core needle biopsy. In the ultrasound-guided group, the participating radiologist performed preoperative ultrasonography to assess tumor location and margin. For small superficial tumors, preferably a 15–7 MHz hockey stick linear array transducer was used connected to a Philips iU22 ultrasound machine, while tumors with more distance to the skin were imaged with a 12–5 MHz linear array transducer. The 15–7 MHz transducer has a substantial smaller surface allowing better manipulation within the small surgical field and a higher spatial resolution than the 12–5 MHz transducer.

Conventional surgery consisted of (1) palpation-guided BCS in patients with palpable tumors, or (2) preoperative wire-guided localization in patients with nonpalpable tumors.

Peroperative ultrasound-guided procedure

During surgery the patient was supine. The radiologist participated in the ultrasound-guided operation. First, the craniocaudal and mediolateral resection margins were marked on the skin using ultrasound imaging. To achieve adequate margins, the ultrasound transducer was applied in the wound to monitor the location of the tumor and its margins. The pectoral fascia was defined as the posterior margin without ultrasound guidance.

After excision, the specimen was examined using ultrasound ex vivo to determine whether or not the tumor was completely excised. If the margin appeared inadequate, additional breast tissue could be excised and sutured to the corresponding side of the specimen. Next, resection planes were marked by sutures for optimal analysis of the margin status. The specimen was directly delivered to the pathologist without the need for specimen mammography.

Procedural time

Surgery time was defined as the period of time the patient was present in the surgery room. Time allocation of the participating radiologist was defined as the period the radiologist was away from the radiology department.

Specimen volume calculation

Assuming an ellipsoidal shape of both the invasive tumor and excised specimens, their volumes were calculated using the formula $4/3\pi r^3$, with r being the radius [11, 14, 15]. Consequently, the theoretical specimen volume (TRV) was calculated by $4/3\pi(\frac{1}{2}a \cdot \frac{1}{2}b \cdot \frac{1}{2}c)$, with a, b, and c representing the three specimen dimensions [11]. Tumor size and specimen dimensions were retrieved from the pathology report. The optimal resection volume (ORV) was calculated using the tumor radius plus an arbitrarily chosen optimal tumor-free resection margin of one cm by $4/3\pi(r + 1.0)^3$ [8, 11]. The relative amount of excessively excised breast tissue, defined by the calculated resection ratio (CRR), was calculated by dividing the TRV by the ORV (CRR = TRV/ORV) [11, 14, 15, 21, 22].

Table 1 Baseline patient and tumor characteristics

	Ultrasound-guided ($n = 66$)	Conventional ($n = 68$)	p
Age (years)	61 (11)	63 (9)	0.22
Palpable	21 (32 %)	24 (35 %)	0.72
Tumor size (cm)	1.5 (0.7)	1.7 (0.8)	0.39
Palpable ($n = 21$ resp 24)	2.1 (0.7)	2.0 (0.9)	0.98
Non-palp ($n = 45$ resp 44)	1.3 (0.6)**	1.4 (0.7)***	0.32
Histology			
IDC	56 (85 %)	62 (92 %)	0.49
LC	6 (9 %)	3 (4 %)	
Other	4 (6 %)	3 (4 %)	

Variables are expressed as mean and SD, or n (%)

Palpable tumors were significantly larger than nonpalpable lesions within the treatment groups (Student's t test, ** $p < 0.001$, *** $p = 0.003$)

IDC infiltrating ductal carcinoma, *ILC* infiltrating lobular carcinoma

Margin status

The margin status was categorized as clear surgical margins (no tumor cells in the inked surface of the resection), 'focally positive' margins (tumor in a limited area of the inked surface, i.e., one or two foci of tumor, maximum of 4 mm), and 'positive' margins (>4 mm of tumor at the margin), according to the Dutch breast cancer guidelines [6, 7]. Reexcision or mastectomy was performed in cases of positive margins [6]. In cases of focally positive margins, additional boost radiotherapy is usually indicated [1, 6, 9].

The primary outcome was excess volume resection as defined by the volume of the resected specimen and the calculated resection ratio (CRR). The optimal CRR is one; higher values indicate less optimal resection volumes with excessive healthy breast tissue excision. The secondary outcome was the surgical procedure time.

Further subgroup analysis was performed with regard to tumor size, palpability of the tumor, and histological type of the tumor. These were retrieved from patient records.

Statistical analysis

Baseline patient and tumor characteristics were described as medians and interquartile ranges (IQRs), or numbers and percentages. We compared baseline characteristics and outcomes between the two treatment groups with the Mann–Whitney-U test and Chi-squared test, or Fisher's exact test in case of small numbers (<5). Multivariate linear regression analysis was applied to test the independent relation between the treatment groups and the outcome resected specimen volume or CRR, adjusted for palpability. The relative risk for re-excision or mastectomy was calculated with its 95 % confidence interval. Differences were considered statistically significant at $p < 0.05$. All data were analyzed with the Statistical Package for the Social Sciences (SPSS statistical software, Version 15.0; SPSS, Inc., Chicago, IL, USA).

Results

A total of 134 women were included, 66 patients in the ultrasound-guided breast-conserving surgery (USG) group, and 68 patients in the conventional breast-conserving surgery (CON) group. In the latter group, 24 patients (35 %) underwent palpation-guided breast-conserving surgery (PAG) and 44 patients (65 %) underwent wire-guided localization breast-conserving surgery (WIG). The patient and tumor characteristics were comparable between the USG and the CON groups (Table 1). The tumor was palpable in 21 of the 66 patients (32 %) in the USG and 24 of the 68 patients (35 %) in the CON group. Tumor size was comparable between the USG and the CON groups. Palpable lesions were larger than the nonpalpable lesions (2.1 vs 1.3 cm; Table 1).

Invasive ductal carcinoma (IDC) was observed in the vast majority of both groups (Table 1). Invasive lobular carcinoma (ILC) was observed in 9 and 4 %, respectively, whereas, the subgroup "other tumors" consisted of tubular or mucinous carcinomas. Tumor-associated unexpected ductal carcinoma in situ (DCIS) diagnosed at pathological examination of the specimen was present in 14 of the 66 specimens (21 %) in the USG group and 16 of the 68 specimens (24 %) in the CON group ($p = 0.75$). Multifocal disease was present in one patient (2 %) in the USG group and in two patients (3 %) in the CON group ($p = 0.58$).

Excision specimen volume and resection margin

Excision volume and CRR was not available in two patients (both in the CON group; one with a palpable and

Table 2 Surgical outcome: specimen volume, calculated resection ratio (CRR), smallest tumor-free margin in cases of clear margin, and margin status

	Ultrasound-guided ($n = 66$)	Conventional ($n = 68$)[a]	p
Specimen volume (cm^3)	39 (20–66)	56 (38–94)	0.02
CRR	1.7 (1.0–2.9)	2.8 (1.4–4.6)	0.12
Smallest tumor-free margin in cases of clear margin (mm)	4 (2–5)	2 (1–4)	0.001
Margin status			0.91
Clear	58 (88 %)	58 (86 %)	
Focally positive	4 (6 %)	5 (7 %)	
Positive	4 (6 %)	5 (7 %)	

Variables are expressed as medians (interquartile ranges) or as n (%)

[a] Excision volume could not be retrieved from pathology reports in two patients in the conventional group; therefore, the number of patients for specimen volume, and CRR is 66

one with a nonpalpable lesion) because it was not adequately noted in the pathology report.

Median excision specimen volume was smaller in the USG group than in the CON group [39 cm^3 (IQR 20–66) vs 56 cm^3 (38–94); $p = 0.02$; Table 2]. Median CRR was also smaller in the USG group (1.7 (1.0–2.9) vs 2.8 (1.4–4.6), respectively ($p = 0.12$)]. The median smallest tumor-free margin was larger in the USG group compared with the CON group [4 mm (2–5 mm) vs 2 mm (1–4 mm), $p = 0.001$].

Tumor-free, clear resection margins were achieved in 58 patients (88 %) of the USG group and in 58 patients (86 %) of the CON group ($p = 0.91$; Table 2).

Reexcision or mastectomy due to positive margins was needed in four patients (6.1 %) in the USG group and in five patients (7.2 %) in the CON group ($p = 1.00$). The relative risk of a positive margin in the USG group compared with the CON group was 0.82 (95 % CI 0.23–2.93).

The smaller excision specimen volumes and CRR in the USG compared with the CON group were irrespective of the fact whether the tumor was palpable or not. Multivariate regression analysis showed that the regression coefficient for resection volumes on USG vs CON was 21.6 (95 % CI: 5.7–37.4, $p = 0.008$), adjusted for palpability. The regression coefficient for CRR on USG vs CON was 1.3 (95 % CI: 0.3–2.2, $p = 0.008$), adjusted for palpability. Data are shown in Table 3.

Tumor histology and margin status

Clear margins were found in 51 patients with an invasive ductal carcinoma in the USG group. In two patients, they were focally positive, and in three they were positive. In the CON group, the corresponding numbers were 55, four, and three.

Of the patients with an infiltrating lobular carcinoma, three had a clear margin, two were focally positive, and one was positive in the USG group. In the CON group, the corresponding numbers were two, one, and zero.

Of the patients with an "other type" carcinoma, four had clear margins, none were focally positive, and none were positive in the USG group. In the CON group, the corresponding numbers were one, zero, and two.

Time allocation

There was no statistically significant difference in median surgery time: 102 (89–123) minutes for the USG group and 94 (78–101) minutes in the CON group ($p = 0.13$). Median time allocation for the participating radiologist was 53 (50–70) minutes based on 49 observations in the USG group.

Discussion

The results of this study demonstrate that ultrasound-guided breast-conserving surgery results in lower excision specimen volumes and resection of less-healthy breast tissues in patients with early-stage invasive breast cancer. This holds true in patients with palpable as well as nonpalpable lesions. In our cohort, the surgical outcome in terms of complete excision of the tumor using ultrasound-guided breast-conserving surgery is not different from that using palpation-guided or wire-guided localization breast-conserving surgery.

Reduction of excision volume has not frequently been the subject of studies on ultrasound-guided breast-conserving surgery. Recent meta-analyses could not demonstrate the reduction of the excision volume as a benefit of the ultrasound-guided breast-conserving surgery [17, 19]. Methodological differences make the studies difficult to compare. The studies that measured the excision volume mostly reported smaller excision volumes when using ultrasound-

Table 3 Surgical outcome: specimen volume, calculated resection ratio (CRR), and margin status

	Palpable lesion ($n = 45$)[a]		p	Nonpalpable lesion ($n = 89$)[a]		p
	Ultrasound-guided ($n = 21$)	Conventional ($n = 24$)[a]		Ultrasound-guided ($n = 45$)	Conventional ($n = 44$)[a]	
Specimen volume (cm^3)	39 (17–71)	50 (37–113)	0.22**	39 (20–64)	64 (39–90)	0.02**
CRR	0.9 (0.7–1.9)	1.6 (1.2–3.2)	0.04***	2.3 (1.2–3.3)	3.2 (1.8–5.9)	0.02***
Margin status			0.40			0.84
Clear	19 (90 %)	20 (83 %)		39 (86 %)	38 (86 %)	
Focally positive	0	2 (8 %)		4 (9 %)	3 (7 %)	
Positive	2 (10 %)	2 (8 %)		2 (4 %)	3 (7 %)	

Variables are expressed as medians (interquartile ranges) or as n (%)

[a] Tumor and excision volume could not be retrieved from pathology reports in one patient with a palpable lesion in the conventional group and one patient with a nonpalpable lesion in the conventional group; therefore, the numbers of patients for tumor size—specimen volume and CRR—are 23 and 43, respectively

**The regression coefficient for specimen volumes on USG vs CON was 21.6 (95 % CI: 5.7–37.4, $p = 0.008$), adjusted for palpability

***The regression coefficient for CRR on USG vs CON was 1.3 (95 % CI: 0.3–2.2, $p = 0.008$), adjusted for palpability

guided surgery compared with conventional surgery, but the differences were small and did not reach statistical significance [11, 13, 14, 23–28]. Barentsz et al., however, found that less-excessive healthy tissue was removed in patients with nonpalpable cancers, since the CRR was significantly lower in the ultrasound-guided group (CRR 3.3 vs 4.3, $p = 0.02$) [14]. In patients with palpable lesions, Krekel et al. were the first to demonstrate that significantly less tissue could be removed (38 vs 57 cm^3, $p = 0.002$), and less-excessive healthy tissue (CRR 1.0 vs 1.7, $p = 0.0001$), even in combination with a higher tumor negative resection margin (97 vs 83 %), using ultrasound-guided surgery [15]. Their reductions in the excision volume and CRR are in the same range as in our palpable lesion group. Our study thus demonstrates that a significant lower excision volume is achievable using ultrasound-guided breast-conserving surgery in patients with palpable and also, for the first time significantly, in nonpalpable tumors without compromising tumor margin status.

Margin statuses were similar in the ultrasound-guided and conventional surgery groups, which are in agreement with a recent study of Barentsz et al. in 258 patients with nonpalpable lesions (93 vs 93 % tumor negative margin) [14], Snider (82 vs 82 % tumor negative margin) [13], Morris [29], and Eggemann (88 vs 87 % tumor negative margin) [28]. In many other studies, USG leads to an improvement in tumor negative resection margin compared with conventional breast-conserving surgery, ranging from 95 to 82 % [11, 15–17, 19, 26, 30]. In some of these studies, tumor negative resection margins in the control group, however, were as low as 71–72 %. This may contribute to the significant difference with the ultrasound-guided surgery group [25, 26]. In our control group this was substantially higher (85 %). In other studies, the resected volume was substantially higher in comparison to our study and ranged from 104 to 119 cm^3 [25, 27]. Eggemann et al. found a near significant relation between a larger excision volume and negative margins: 117 vs 81 mm^3, in the tumor negative and tumor positive margin group, respectively ($p = 0.07$) [26].

Our rate of tumor negative resection margin using ultrasound-guided surgery (88 %) was in the middle-to-lower range compared to those of other studies [15, 16, 26, 28–31]. Results of resection margin status of various studies are difficult to compare because of heterogeneity in patients, tumor characteristics, interpretation of margin statuses, and ultrasound techniques. The infiltrating lobular carcinoma histologic subtype, for instance, has been reported to be less conspicuous not only on mammography, but also on ultrasound [32–34]. Eggemann et al. found a higher rate of positive resection margins in infiltrating lobular carcinoma compared to ductal carcinomas [26]. This could negatively influence intrasurgical guidance and thus resection margin status. In the studies of Moore et al. and Krekel et al. with high tumor negative resection margins (94 and 97 %, respectively), the percentages of ILC were low (0 and 2 %, resp), whereas in our study and Eggemann et al.'s study with 88 % tumor-free margin, the percentage of ILC was 9 %. The decreased conspicuity of lobular-type carcinoma on ultrasound, as well as an assumed detrimental effect on margins status, is not univocal [16, 35].

Moreover, the definition of a positive resection margin remains an international subject of debate [7]. We identified patients with focally positive margins (<4-mm tumor-involved margin) as a separate group (i.e., not included in the clear margin group). These patients do not require re-excision according to the Dutch breast cancer guideline

[6, 7]. Our re-excision rate of 6 % in ultrasound-guided and conventional surgery group is in the lower range compared with other studies ranging from 11 to 23 % [14, 26, 31] and is well within the standards of Dutch breast cancer guideline [6, 7]. If we would include the focally positive resection margin in the negative group, a tumor negative resection margin would be achieved in 94 % in the ultrasound-guided and 93 % in the conventional surgery group.

Another factor that could influence a resection margin status could be tumor size. Median tumor size in the group of tumor positive margins was larger than in the group with negative margins [USG: 3.1 cm (IQR 1.8–3.5; $n = 4$) vs 1.5 cm (0.9–1.9; $n = 58$); $p = 0.13$] and CRR was lower [USG: 1.0 (0.8–1.7) vs 1.8 (1.1–2.9); $p = 0.04$]. This suggests that despite the US guidance, the surgeon is tempted to resect too small a volume in case of a large tumor. On the other hand, CRR is relatively large in the nonpalpable compared with the palpable USG group (Table 3), suggesting that these small lesions are resected amply. This higher CRR in the nonpalpable group is, however, not accompanied by a larger percentage of negative resection margins, indicating that the relation between tumor size and clear resection margins is complex. Our study group is too small to analyze this subject with proper statistical analysis. The relation between tumor size and margin status could form the subject of future studies.

A possible disadvantage in the application of ultrasound-guided BCS for daily radiological practice is the requirement of a radiologist in the operating room to assist in the procedure if the surgeon is not trained to do so. The observed median time allocation for the participating radiologist of 53 (50–70) minutes is substantial and can be logistically challenging in a busy radiology department. Therefore, we recently initiated a hands-on training period for dedicated radiographic breast-imaging assistants to perform the intraoperative ultrasound-guided procedure under direct preoperative supervision of a participating radiologist. Also, a dedicated breast surgeon can be trained to perform the ultrasound by themselves [15, 26].

An important limitation of our study is that we compared a prospectively assembled cohort to a historical cohort, which introduces potential sources of bias, therefore limiting the level of evidence. Furthermore, we did not evaluate cosmetic results and patient satisfaction after ultrasound-guided breast-conserving surgery. A greater depth of information may have been obtained by a standardized questionnaire used to assess patient satisfaction and surgeons' score on cosmetic outcomes. Also, information regarding breast density, size, and tumor location was not assessed in this study. Next to tumor factors or surgery techniques, these patient characteristics have been shown to be associated with cosmetic outcome and tumor-involved resection margins [20, 36].

In conclusion, our study shows that ultrasound-guided breast-conserving surgery results in lower excision volumes and resection of less-healthy breast tissue in patients with early-stage invasive breast cancer, without compromising margin status in palpable as well as nonpalpable lesions, although our results may be influenced by potential bias.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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